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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,846	01/13/2000	DAVID A. ESTELL	GC381-US	5580

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/30/2002 15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,846	ESTELL, DAVID A.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-21 are pending in the application.

Applicants' amendment to the specification and claims 1, 4-7, 9, 13-17 and addition of claims 18-21 in Paper No. 14, filed 05/17/02 is acknowledged.

Claims 2, 3, and 10-12 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicants' arguments filed in Paper No. 14 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

1. It is noted that an Information Disclosure Statement (Form PTO-1449) has been filed as Paper No. 15. However, references marked with an asterisk ("*") and the reference cited on page 3 of the IDS as "Webb Academic Press, Inc., editor, Enzyme Nomenclature, 1992" are not present with the references submitted in Paper No. 15 and therefore, cannot be considered as per applicants' request. It is noted that applicants state in Paper No. 15 that references marked with an asterisk have not been submitted and will therefore not be considered. Also, the examiner has made an earnest attempt to locate reference cited as "Webb Academic Press, Inc., editor, Enzyme Nomenclature, 1992" without success. If applicants would like the examiner to consider the cited references, it is suggested that copies of the missing references be submitted and upon receipt, the examiner will consider the references and return Form PTO-1449 in a subsequent communication.

Claim Objections

2. In view of applicants' amendment to claims 15, 17, and 21 to identify the apr, npr, epr, and mpr genes as genes encoding apr, npr, epr, and mpr proteases, respectively, and in light of the specification, the objection is withdrawn. Based on applicants' amendment and in light of the instant specification, one of skill in the art would recognize the protease for which each abbreviation is used, i.e., apr for alkaline protease, npr for neutral protease, epr for extracellular protease, and mpr for metalloprotease. These abbreviations are recognized in the art (see for example, Sloma et al. *J Bacteriol* 173:6889-95, abstract). However, based on the prior art, it is unclear as to what specific protease the abbreviation "wpr" refers. The examiner can find no teaching for the common use of the abbreviation "wpr" for a specific protease in the prior art. It is noted that applicants have submitted an IDS reference (Margot et al. *Microbiol* 142:3437-3444) that uses the abbreviation "wprA" for Bacillus subtilis 168, a cell wall-associated protease. However, it is unclear from the specification and the prior art as to whether "wpr protease" is the same protease as "wprA". Therefore, the objection to the use of the abbreviation "wpr protease" is maintained for the reasons of record and the reasons discussed above.

3. Claim 13 is objected to because of the following informalities: the term "comprising nucleic acid" in line 3 is grammatically incorrect and should be replaced with, for example, "comprising a nucleic acid" and the term "cystein" in line 6 is misspelled and should be replaced with, for example, "cysteine". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 (claim 21 dependent therefrom) is indefinite in the recitation of "*Bacillus* comprises the nucleic acid sequence set forth in SEQ ID NO:1". As written, it is unclear as to whether the gene encoding SEQ ID NO:2 of claim 13 is meant to be interpreted as SEQ ID NO:1 or some other gene. The examiner has interpreted claim 20 as meaning the gene encoding SEQ ID NO:2 is SEQ ID NO:1. If the

examiner's interpretation of the claim is incorrect, applicant should so state and clarify the record. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

5. The written description rejection of claims 16-19 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Applicants argue the claims as amended meet the written description requirement as claim 18 recites the nucleic acid of SEQ ID NO:1. Applicants' argument has been fully considered but is not found persuasive to overcome the instant rejection.

It is noted that claim 16 has not been amended to recite the structure of the gene encoding CP1. Also, while claim 18 has been amended to recite the CP1 gene of SEQ ID NO:1, the claim encompasses *all* gram-positive microorganisms with a mutation or deletion of SEQ ID NO:1 with no defined function. The specification teaches only one representative species of such gram-positive microorganisms or *Bacillus* host cells, namely, *Bacillus subtilis* with a deletion in the gene encoding SEQ ID NO:2 or a deletion of the polynucleotide of SEQ ID NO:1, resulting in the inactivation of CP1 proteolytic activity. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of gram-positive microorganisms, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus that distinguish the species within the genus from other gram-positive microorganisms such that one can visualize or recognize the identity of the members of the genus. The specification fails to disclose any other gram-positive microorganisms by any

identifying structural characteristics or properties other than the functionality of having a mutation or deletion in at least one of the genes encoding CP1 (claim 16) and optionally wherein the gram-positive microorganism further comprises a mutation or deletion of apr, npr, epr, wpr, and mpr (claim 17), and optionally wherein the gram-positive microorganism further comprises a mutation or deletion of apr, npr, epr, wpr, and mpr (claim 19). The specification provides no disclosure of other species of gram-positive microorganisms having a mutation or deletion in at least one of the genes encoding CP1 or SEQ ID NO:1 from any gram-positive microorganism other than a *Bacillus* host cell. Regarding claim 18, no description has been provided of the gram-positive microorganism having mutations of SEQ ID NO:1. No information, beyond the characterization of SEQ ID NO:1 has been provided by applicants which would indicate that they had possession of the claimed genus of gram-positive microorganisms comprising mutations of SEQ ID NO:1. The specification does not contain any disclosure of the function of the encoded proteins of a mutant SEQ ID NO:1, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides that can have a wide variety of functions. Therefore many functionally unrelated genes comprised by a gram-positive microorganism are encompassed within the scope of these claims. Given the lack of description of additional representative species of microorganisms as encompassed by the genus of the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

6. The scope of enablement rejection of claims 1, 4-9, and 13-21 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Applicants argue the claims as amended are enabled by the specification as claims 1 and 13 have been amended to recite the polypeptide of SEQ ID NO:2 and new claims 18 and 20 recite the nucleic acid of SEQ ID NO:1. Applicants' argument has been fully considered but is not found persuasive to overcome the instant rejection.

The specification is enabling for a *Bacillus subtilis* host cell with a deletion of a gene encoding the polypeptide of SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1, thereby resulting in the inactivation of

CP1 proteolytic activity and a method for producing a heterologous protein using a *Bacillus subtilis* host cell with a deletion of a gene encoding the polypeptide of SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1, thereby resulting in the inactivation of CP1 proteolytic activity. However, the specification does not support the broad scope of the claims which encompass *any* gram-positive microorganism (claim 1), *any* Bacillus (claim 4), or *any* of the Bacilli listed in claim 5 having *any* mutation or a deletion of a gene encoding SEQ ID NO:2; *any* gram-positive microorganism having *any* mutation or deletion of *any* gene encoding CP1 (claim 16) or the CP1 gene of SEQ ID NO:1 (claim 18), and optionally having *any* mutation or deletion in *any* of the genes encoding apr, npr, epr, wpr, and mrp (claims 17 and 19); or a method of producing a heterologous protein using *any* Bacillus (claim 13) or any Bacilli of claim 14 having *any* mutation or deletion in a gene encoding SEQ ID NO:2 or the CP1 gene of SEQ ID NO:1 and optionally comprising *any* mutation or deletion in *any* of the genes encoding apr, npr, epr, wpr, and mrp (claims 15 and 21) because the specification does not establish: (A) regarding claims 16 and 17, the sequences of CP1 polypeptides or encoding polynucleotides of all gram positive microorganisms, guidance for isolating said sequences from all gram-positive microorganisms, or the predictability that a CP1 gene is present in all gram-positive microorganisms; (B) regions of a CP1 from any gram-positive microorganism, the polypeptide of SEQ ID NO:2, or the polynucleotide of SEQ ID NO:1 that may be mutated with an expectation of obtaining the desired biological activity; (C) regions apr, npr, epr, wpr, and mrp from all gram-positive microorganisms or Bacillus hosts that may be mutated with an expectation of obtaining the desired biological activity; (D) the predictability that all gram-positive microorganisms or Bacillus hosts will possess a gene encoding SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1 as an undue amount of experimentation would be required to examine all gram-positive microorganisms for the presence of a gene encoding SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24

(CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

7. The rejection of claims 1, 4-9, and 13-21 under 35 U.S.C. 102(b) as being anticipated by WO89/10976 is maintained. The rejection was fully explained in a previous Office action.

Applicants argue WO89/10976 does not teach an organism with a mutation or deletion of part or all of the gene encoding CP1 or an organism with a mutation or deletion of part or all of the gene encoding CP1 with additional mutation(s) or deletion(s) in at least one of the genes encoding apr, npr, epr, wpr, and mpr proteases. Applicants argue WO89/10976 does not teach every limitation provided in the claims and therefore, the reference does not anticipate the claimed invention. Applicants state, "in order to further prosecution of the present application and Applicant's business interests, the independent Claims have been amended to recite SEQ ID NO:2". Applicants' argument has been fully considered, but is not found persuasive to overcome the instant rejection.

It is noted that independent claim 16 does not recite the limitation of "SEQ ID NO:2" and is broadly interpreted as a gram-positive microorganism having a mutation or deletion of a gene encoding *any* CP1. In response to applicants' argument, applicants have provided no evidence to distinguish CP1 or the polypeptide of SEQ ID NO:2 encoded by SEQ ID NO:1 from the cysteine protease of WO89/10976 nor have applicants distinguished the cysteine protease-deficient AP^-/NP^- B. subtilis mutant of WO89/10976 from the claimed microorganisms. In the absence of such distinguishing evidence, it is unclear as to how the cysteine protease-deficient AP^-/NP^- B. subtilis mutant and methods of use thereof for expressing a heterologous protein as taught by WO89/10976 differ from the claimed microorganism and methods of use thereof. While applicants have amended independent claims 1, 13, 18, and 20 to recite the limitation of SEQ ID NO:2 or SEQ ID NO:1, this limitation does not distinguish the claimed microorganisms and methods of use thereof from the cited prior art as the cysteine protease-deficient AP^-/NP^- B. subtilis of the

prior art would inherently have a mutated sequence of SEQ ID NO:1 due to homologous recombination resulting in inactivation of cysteine protease activity. Since the Office does not have the facilities for examining and comparing applicants' microorganisms with the microorganism of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the microorganism and method of use thereof for expressing a heterologous protein of the prior art does not possess the same material structural and functional characteristics of the claimed microorganisms and method of use thereof). See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594. Therefore, the rejection is maintained for the reasons of record and for the reasons discussed above.

Conclusion

8. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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